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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SZPERKA, MICHAEL EDWARD

ART UNIT

PAPER NUMBER

1644

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/805,881	WELLS, IBERT C.
	Examiner	Art Unit
	Michael Szperka	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 23 August 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-19 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____.
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>3/22/04 & 5/10/04</u> .	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, the peptide species SEQ ID NO: 2, and the species preeclampsia as a physiological disorder in the reply filed on August 23, 2004 is acknowledged.

A method of assessing a predisposition to preeclampsia by detecting a significantly lower level of a tachykinin peptide in a body fluid as compared to a standard appears to be free of the prior art, and therefore the search has been extended to other recited physiological disorders.

Claim 1 has been amended.

Claims 20-30 have been canceled.

Claims 1-19 are currently pending in this application.

Claims 1-19, a method of measuring a tachykinin peptide comprising SEQ ID: 2 in a body fluid as they read a physiological disorder associated with magnesium binding defect are under consideration in the instant application.

Priority

2. Under 35 U.S.C. 120, a claim in a U.S. application is entitled to the benefit of the filing date of an earlier filed U.S. application if the subject matter of the claim is disclosed in the manner provided by 35 U.S.C. 112, first paragraph in the earlier application. See MPEP 201.11. In response to restriction and species election requirements, applicants have chosen to prosecute a method of assessing a

predisposition to the physiological disorder preeclampsia that is associated with magnesium binding defect in an individual. Preeclampsia is not disclosed as being associated with a magnesium binding defect in U.S. Patent 6,372,440, but it is disclosed in U.S. Patent 6,455,734. Therefore, the priority date for claims 2-6 is August 9, 2000, the priority date for U.S. Patent 6,455,734, while the priority date for claims 1 and 7-19 is March 10, 1999, the priority date for U.S. Patent 6,372,440.

Additionally, the first line of the specification should be amended to indicate that U.S.S.N. 10/230,133 has issued as U.S. Patent No. 6,664,420, and to indicate the relationship of the instant application to U.S.S.N. 10/695,536, filed on 10/28/03.

Specification

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The term enzyme-linked immunosorbant assay appears in the originally filed claims 6, 11, and 17, but not in the specification. The specification should be amended to provide appropriate antecedent basis for these claims.

The disclosure is objected to because of the following informalities:

On page 8, tachykinins is misspelled.

Appropriate correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is

requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-19 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

The omitted steps are a complete means for measuring the level of a peptide in all pending claims, a means for distinguishing between salt-sensitive and salt resistant hypertension in claim 12, and a means for distinguishing between lipid induced and magnesium binding defect associated type II diabetes in claim 18. Incorporation of limitations found in separate dependent claims, specifically the reagents and steps needed to detect the peptide sequences, into the base claim may be useful in obviating some of the rejections.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6 and 13-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the detection of a lower than normal level of a tachykinin peptide in a body fluid being associated with essential hypertension, does not reasonably provide enablement for the detection of a lower level of a tachykinin peptide in a body fluid being associated with type 2 diabetes or preeclampsia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has claimed a method of performing an immunological assay to detect a peptide derived from the C terminal amino acid sequence that is found in all mammalian tachykinins (FXGLM, where X is either F or V (SEQ ID NO: 4)), wherein the detection of a lower than standard level of said peptide is indicative of a physiological disorder associated with the magnesium binding defect. The detected peptides FFGLM (SEQ ID NO: 1 and one of the possibilities of SEQ ID NO: 4) and FGLM (SEQ ID NO: 2) are found in substance P (SP), while FVGLM (the other possibility for SEQ ID NO: 4) is found in neurokinin A (NKA) and neurokinin B (NKB).

Applicant has disclosed that the physiological disorders salt-sensitive hypertension, type 2 diabetes and preeclampsia are associated with the magnesium binding defect in an individual. Evidence for this association is the presence of erythrocytes deficient for plasma membrane bound magnesium in hypertension (Examples 1, 2, 3, and 8), diabetes (Example 8) and preeclampsia (Example 4) as measured by atomic absorption spectrophotometry (paragraph 117). Evidence is also disclosed that incubating erythrocytes that have a lower than normal amount of cell

membrane associated magnesium with the peptides FFGLM or FGLM leads to an increase in the amount of magnesium bound by the plasma membrane (Examples 2-3 (hypertension), 5 (preeclampsia), and 7 (artificially induced magnesium deficiency), although it is noted that Example 5 is prophetic). It does not appear that Applicant has measured the level of these tachykinin peptides in patient samples and then correlated the tachykinin levels to the level magnesium bound as determined by atomic absorption spectrophotometry. However, a correlation between low plasma levels of SP and hypertension has been reported in a rat model of hypertension (Mori et al., Jpn. Heart J., 1993, 34:785-794) and humans diagnosed with hypertension (Faulhaber et al., J. Cardiovascular Pharmacology, 1987, Vol. 10 (Suppl. 12): S172-S176).

Correlation between tachykinin levels in body fluids and the physiological disorders type 2 diabetes and preeclampsia is not as clear. Sanfilippo et al. (J. Reprod. Med., 1992, 37:733-736) indicate that the level of SP in amniotic fluid is increased in diabetic patients as compared to controls (see entire document, Table 1 in particular). Page et al. (Nature, 200, 405:797-800) indicate that the level of neurokinin B in the plasma of patients diagnosed with preeclampsia was significantly increased over the levels measured in control patients (see entire document, particularly Figure 2). As such, it is not clear that a determination of a below normal level of a tachykinin peptide comprising SEQ ID NO: 1, 2, or 4 in a body fluid sample taken from a patient is predictive of any physiological disorder other than salt-sensitive essential hypertension. The scope of enablement must bear a reasonable correlation with the scope of the claims. In light of the unpredictability of correlating tachykinin levels to physiological

disorders other than salt-sensitive hypertension, undue experimentation would be required by persons of skill in the art to practice the full breadth of the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 7, 8, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Faulhaber et al. (J. Cardiovascular Pharmacology, 1987, Vol. 10 (Suppl. 12): S172-S176, see entire document).

Faulhaber et al. teach the measurement of SP in the serum plasma of patients diagnosed with essential hypertension using a radioimmunoassay (RIA, see S173, left column, second full paragraph). Faulhaber et al. then compare this value with the level of SP found in normotensive controls and teach that the level of plasma SP is lower in patients that have been diagnosed with essential hypertension (see particularly, Abstract, Figure 1, and Conclusion). Additionally, Faulhaber et al. demonstrate that the level of SP increases and blood pressure decreases in hypertensive patients after treatment for two weeks with the anti-hypertensive drug prazosin and captopril (see particularly Figure 5 and the paragraph that spans S173 to S176). It is unknown if the patients described by Faulhaber et al. were being treated for salt-sensitive or salt-insensitive hypertension. Applicant is invited to present evidence that the patients of

Faulhaber et al. were not suffering from salt-sensitive hypertension. See In re Best, 195 USPQ 430 (CCPA 1977), and MPEP 2112. Therefore, the teachings of the prior art anticipate the claimed invention.

10. Claims 1, 7, 8, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Mori et al. (Jpn. Heart J. 1993, 34:785-794, see entire document).

Mori et al teach the measurement of SP in the serum of spontaneously hypertensive stroke prone rats (SHRSP) and the control strain WKY and by an enzyme linked immunoassay and demonstrate that SHRSP animals have a deficiency of serum SP (see entire document, particularly Figure 1 and page 789, section titled SP Concentration in Plasma of Rats). Hypertension in SHRSP animals is exacerbated by excessive salt intake, and strain SHR (spontaneous hypertensive rat) from which SHRSP is derived is a model for salt-sensitive essential hypertension.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claims 1 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulhaber et al. (J. Cardiovascular Pharmacology, 1987, Vol. 10 (Suppl. 12):

S172-S176, see entire document) in view of Couraud et al. (J. Neurochemistry, 1987, 49:1708-1718, see entire document).

The teachings of Faulhaber et al. have been discussed above. Faulhaber et al. do not teach the use of a monoclonal antibody in their SP detection assay, nor is their assay an enzyme-linked immunosorbant assay.

Couraud et al. teach the production and purification of monoclonal antibodies specific for SP, and their use in RIA and EIA (enzyme immunoassay) experiments (see Methods and Materials, page 1709-1711, especially the sections labeled Production and purification of mAbs, EIA for SP, and RIA). The monoclonal antibodies generated by Couraud et al. are capable of detecting the presence of SP, NKA and NKB (see Table 3 in particular). Couraud et al. also teach that EIA is preferable to RIA because it avoids the problems of radioactive, short-lived tracers, and reduces handling time, thus increasing the throughput of the assay (page 1717, left column, fifth full paragraph). Additionally, it is taught that monoclonal antibodies are preferred over polyclonal antibodies because monoclonal antibodies can be produced in large quantities for use in the complete characterization of a given model system (page 1709, left column, 9 lines from the top, sentence starting "However, ...").

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the monoclonal antibody EIA of Couraud et al. for the RIA of Faulhaber et al. because of the advantages of avoiding radioactivity and increased assay throughput in the EIA, and the advantage of the increased amount of antibody available for experiments gained by using a monoclonal antibody rather than a

polyclonal serum. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

13. Claims 1 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al. (Jpn. Heart J. 1993, 34:785-794, see entire document) in view of Couraud et al. (J. Neurochemistry, 1987, 49:1708-1718, see entire document).

The teachings of Mori et al. have been discussed above. Mori et al. do not teach the use of a monoclonal antibody in the enzyme immunoassay to detect SP.

The teachings of Couraud et al. have also been discussed above.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the monoclonal antibody of Couraud et al. for the polyclonal serum of Mori et.al. because of the increased amount of antibody that can be obtained for use in experimental procedures. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,372,440. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of U.S. Patent No. 6,372,440 anticipate the broader scope of instant claims 1-19.

16. No claims are allowable.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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